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REVIEW ARTICLE

Implications of Adverse Outcomes Associated with Antipsychotics in Older Patients with Dementia: A 2011–2022 Update

Marianna Rogowska[1] · Mary Thornton[1] · Byron Creese[2,3] · Latha Velayudhan[1,2] · Dag Aarsland[1,4] · Clive Ballard[2,4] · Konstantinos Tsamakis[1,5] · Robert Stewart[1,2] · Christoph Mueller[1,2]

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Abstract

Neuropsychiatric symptoms affect most patients with dementia over the course of the disease. They include a wide variety of symptoms from apathy and depression to psychosis, irritability, impulsivity and agitation. These symptoms are associated with significant distress to the patient and caregivers, as well as more rapid progression of dementia, institutionalisation and higher mortality. The first-line management of the neuropsychiatric symptoms of dementia should be non-pharmacological. If medications are required, antipsychotics are commonly chosen. Second-generation antipsychotics such as risperidone, olanzapine, quetiapine and aripiprazole are prescribed more often than first-generation antipsychotics, such as haloperidol. The aim of this review is to provide an update on findings on adverse outcomes and clinical implications of antipsychotic use in dementia. These medications may increase mortality and can be associated with adverse events including pneumonia, cerebrovascular events, parkinsonian symptoms or higher rates of venous thromboembolism. Risks related to antipsychotic use in dementia are moderated by a number of modifiable and non-modifiable factors such as co-prescribing of other medications, medical and psychiatric co-morbidities, and demographics such as age and sex, making individualised treatment decisions challenging. Antipsychotics have further been associated with an increased risk of reliance on long-term care and institutionalisation, and they might not be cost-effective for healthcare systems. Many of these risks can potentially be mitigated by close physical health monitoring of antipsychotic treatment, as well as early withdrawal of pharmacotherapy when clinically possible.

1 Introduction

Dementia is a chronic, progressive and incurable syndrome that leads to cognitive and functional decline exceeding that of the natural aging process. The World Health Organization estimates that over 55 million people worldwide live with dementia [1]. That number is growing, and it is predicted that by the year 2050, 132 million people worldwide will be affected [2].

Dementia care requires significant financial expenditure. In 2015 it was estimated to be US$818 billion—the equivalent of 1.1% of the world gross domestic product. Given the predicted increase in dementia cases, this figure is also expected to rise significantly [2]. This increase in

Key Points

Despite limited efficacy, antipsychotics are the most extensively studied pharmacological treatment for the neuropsychiatric symptoms of dementia.

Antipsychotic use in dementia is associated with the risk of various adverse outcomes ranging from sedation to cerebrovascular events and even death, as well as an increased rate of hospitalisations and institutionalisation.

These risks are moderated by a number of modifiable and non-modifiable factors making individualised treatment decisions challenging.

✉ Marianna Rogowska
marianna.rogowska@nhs.net

1 South London and Maudsley NHS Foundation Trust, Bethlem Royal Hospital, Monks Orchard Road, Beckenham, London, UK

2 Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK

3 University of Exeter Medical School, Exeter, UK

4 Stavanger University Hospital, Stavanger, Norway

5 Second Department of Psychiatry, National and Kapodistrian University of Athens, School of Medicine, University General Hospital 'ATTIKON', Athens, Greece

prevalence and financial burden, alongside the fact that there is currently no preventative or curative treatment, highlights a global need for effective management of cognitive symptoms, as well as psychiatric and somatic co-morbidities.

Dementia is not only associated with cognitive decline but also with a range of neuropsychiatric symptoms often referred to as behavioural and psychological symptoms of dementia (BPSD) [3]. These require a different management approach to the cognitive decline. Over the course of dementia, 97% of patients experience one or more symptoms of BPSD [4]; the most common is apathy, affecting nearly half of the patients, and other neuropsychiatric symptoms include depression, agitation/aggression, anxiety, sleep disturbances, irritability, changes in appetite, abnormal motor behaviours, delusions, disinhibition and hallucinations [5]. Neuropsychiatric symptoms can cause significant distress to both patients and their caregivers. They are associated with negative outcomes such as functional impairment, dependence on others for support with their activities of daily living and faster cognitive decline leading to advanced dementia, which is associated with further complications like falls, hospitalisations and early institutionalisation [6, 7].

The aetiology of neuropsychiatric symptoms in dementia is multifactorial. Genetic, biological, psychological, social and neuroinflammatory factors have all been suggested to play a role [6, 8, 9]. Neurodegenerative processes of dementia can affect areas of the brain responsible for cognition and emotions. This leads to the breakdown of brain circuitry affecting a person's ability to interact with their environment, making the patients more vulnerable to internal and external stressors, which, in turn, can affect their functioning, interactions with carers, and manifest as behavioural disturbance [4].

Antipsychotics are commonly prescribed to support the management of agitation and psychosis in dementia, although their use comes with certain risks. In 2005 and 2008 the US Food and Drug Administration (FDA) issued a black box warning due to increased mortality and cerebrovascular events (CVEs) in older adults taking first- and second-generation antipsychotic medications. There are, therefore, no antipsychotics licensed in the USA for the management of agitation and psychosis in dementia [10], while the UK's National Institute for Health and Care Excellence (NICE) recommends their use only after a thorough assessment of risks and benefits, highlighting that in BPSD, the majority of antipsychotics are used off-label [11].

This narrative review aims to provide an update on the adverse outcomes of the use of antipsychotics in older adults living with dementia and the clinical implications of their use. The authors searched the PubMed MEDLINE database with the terms 'dementia OR Alzheimer OR Lewy bodies' and 'antipsychotic OR antipsychotics' and 'side effects OR adverse effects OR adverse outcomes' for articles published over the last 11 years (July 2011 to July 2022). This 11-year time frame was chosen as studies prior to this period have already been comprehensively reviewed [12–14]. The initial search yielded 796 results. These were reviewed for relevance and cross-references were scrutinized. Articles were included if they studied populations with dementia, use of antipsychotics, adverse treatment outcomes and their clinical implications. Selected articles included randomised controlled trials and observational studies with qualitative outcome measures, as well as reviews, systematic reviews and meta-analyses published within the given timeframe. Excluded were case reports and series, as well as studies without focus on dementia, antipsychotics or their adverse outcomes.

2 Antipsychotic Medications Used in Dementia

Despite evidence of only a small effect size [3, 4, 10, 15–20], antipsychotics are often the first-line pharmacological treatment for agitation and psychosis in dementia [16]. Although the numbers may vary between countries and patient groups, nearly one in five patients in a 2011–2013 Swedish study on nursing home dementia patients was prescribed an antipsychotic [21]. Data from the UK show that during the first months of the COVID-19 pandemic (March–June 2020), rates of antipsychotic prescriptions increased [22, 23], which may have been associated with changes in routines of the patients, social isolation, or changes in mental health and social services provision. The reduction of face-to-face contact may have further limited the possibility of implementing non-pharmacological interventions.

The second-generation antipsychotic (SGA) risperidone is most commonly prescribed for agitation (40% of patients in a Danish register study [24]) and has been licensed for use in Europe, Canada, New Zealand and Australia for the management of agitation and aggression in dementia [25]. Other antipsychotics used in clinical practice include olanzapine, aripiprazole, quetiapine (SGAs) and, less commonly, haloperidol, a first-generation antipsychotic (FGA). There are some significant pharmacodynamic differences between FGAs and SGAs. FGAs (e.g., haloperidol, zuclopenthixol, flupenthixol, chlorpromazine) act primarily as antagonists of D_2 receptors in the brain; this mechanism of action has proven highly effective in managing symptoms of psychosis by acting on the D_2 receptors in the mesolimbic system. However, the D_2 antagonism of FGAs in other dopaminergic pathways causes side effects, such as extrapyramidal symptoms, emotional numbing and hyperprolactinaemia. SGAs

are a more pharmacodynamically diverse group; although SGAs also act on D_2 receptors to some degree, different substances from this group present unique receptor profiles including dopamine, histamine, serotonin, muscarinic and adrenergic receptors. Such wide receptor binding properties come with a lower risk of dopaminergic side effects, but are often associated with weight gain, abnormalities in blood glucose and lipid profile, as well as sedation. Additionally, FGAs and many SGAs have been linked to the QTc prolongation on ECG due to interactions with cardiac potassium channels [26, 27].

A 2019 network meta-analysis of placebo-controlled trials with aripiprazole, risperidone, quetiapine and olanzapine use in patients with agitation and psychosis in dementia demonstrated no significant difference between these medications with regard to their clinical effectiveness and adverse outcomes such as death or CVEs [25]. Other studies investigating these antipsychotics have had inconsistent results. In comparison with placebo, olanzapine has not shown effectiveness in improving scores of the Neuropsychiatric Inventory (NPI), Brief Psychiatric Rating Scale (BPRS) or Cohen-Mansfield Agitation Inventory (CMAI) [25]. Findings on the effectiveness of quetiapine have been variable, with one study reporting a statistically significant improvement in BPRS scores [25], whilst other studies found it ineffective [10, 28, 29]. A 2021 systematic review on the use of antipsychotics in dementia found no beneficial effect of quetiapine on agitation and psychosis, and only minimal benefit of use of risperidone for agitation, but not psychosis, when compared to placebo [20]. Risperidone has shown improvement in CMAI scores, focused on agitation, but not in BPRS, which looks at a wider scope of psychiatric symptoms [25, 28]. For SGAs as a group, there is evidence of only a slight reduction of agitation and negligible effect on improving psychosis [20]. Aripiprazole has been found to be ineffective in improving psychotic symptoms of dementia in a 2022 network meta-analysis using the NPI [29]; however, the previous version of this meta-analysis, which assessed outcomes on both psychosis and agitation, reported slight improvement of symptoms in the NPI [25].

Two newer antipsychotic agents have also been evaluated for their efficacy in agitation and psychosis in dementia. Brexpiprazole, a D_2–D_3 and 5-HT_{1A} partial agonist and 5-HT_{2A} antagonist, has shown a modest therapeutic effect on agitation in patients with Alzheimer's dementia (AD) during 12-week trials [30, 31]. However, it was associated with frequent side effects such as headaches, insomnia, dizziness, urinary tract infections and somnolence. No significant differences were found for extrapyramidal side effects, suicidality, QT interval prolongation or metabolic side effects, including weight gain, when compared to placebo. Overall, longer observations are necessary to determine whether brexpiprazole is a safer option than the commonly used SGAs.

Pimavanserin (a selective 5-HT_{2A} inverse agonist) is another potential alternative. The FDA has approved it for treatment of psychotic symptoms in patients with dementia and Parkinson's disease, although it has not been approved in Europe [32, 33]. Pimavanserin may be effective in treating hallucinations and delusions in patients with AD; however, it has no effect on symptoms of BPSD such as apathy, agitation, aggression or disinhibition [34]. A placebo-controlled trial involving 181 nursing home residents with severe dementia [32, 34] reported encouraging short-term results in managing AD-related psychosis, in particular for the more severe subgroup (psychosis score ≥ 12 in Neuropsychiatric Inventory Nursing Home version (NPI-NH)). After 6 weeks of follow-up, 66.7% of patients on pimavanserin 34 mg daily achieved significant NPI-NH psychosis score reductions to less than 6 points, compared to only 32% of placebo controls. After 12 weeks of follow-up, however, 45.5% of both pimavanserin and placebo-treated patients had an NPI-NH score < 6. It is important to note that the incidence of adverse outcomes (such as falls, urinary tract infection, agitation, contusion, aggression or lower respiratory infection) in both groups were similar for placebo and active treatment arms, suggesting good tolerability of pimavanserin in patients with severe dementia [34]. Pimavanserin was further shown to reduce the risk of relapse of psychotic symptoms in a discontinuation trial including patients with dementia-related psychosis, whereby 13% of patients on pimavanserin relapsed versus 28% of those who were switched to placebo after the initial remission of symptoms [35]. This trial was, however, stopped early for efficacy. A longer observation period could have altered the relapse rates in both arms of the trial. Additionally, among the study participants, 15% had Parkinson's disease, which is not representative of the dementia population. This could have skewed the results in pimavanserin's favour, given that it has proven efficacy in treating Parkinson's disease-related psychosis.

3 Antipsychotic-Related Mortality Risks and its Determinants

The use of antipsychotics in people with dementia is associated with increased all-cause mortality [7, 36–38] and stroke-specific mortality [7]. When compared to monotherapy with other psychotropics, antipsychotics have been found to increase short- and long-term mortality nearly twofold [39].

3.1 Type of Antipsychotic and Mortality

FGAs are considered to have a higher mortality risk than SGAs [18], although, Mühlbauer et al. found in their systematic review that the difference in risk between FGAs and SGAs may be smaller than expected, with the relative risk (RR) of death being 1.46 for FGAs and 1.36 for SGAs [20]. Studies on FGAs have been predominantly focused on haloperidol, and there is little evidence of the benefits or harm of other typical antipsychotics. There are certain discrepancies in findings on mortality risk and haloperidol—the above-mentioned work by Mühlbauer et al. found a risk ratio (RR) of 1.88 with 95% confidence interval (CI) 0.65–5.88 suggesting no difference in mortality among older adults with dementia compared to placebo [20], while Ralph et al.'s meta-analysis reported a significant increase of mortality with a hazard ratio (HR) of 2.43 and 95% CI 2.25–2.61 [36]. This has been supported by other studies that found haloperidol to increase mortality compared to placebo [40] and other antipsychotics [18, 36, 39, 41, 42] (HR = 1.71 [36]). The discrepancy may be due to differences in studies included in both metanalyses—Mühlbauer et al. [20] collected data from randomised controlled trials, while Ralph et al. [36] also included information from European databases. One study comparing mortality for patients on FGAs and SGAs found that FGAs were associated with higher mortality due to stroke (6.7%, RR = 1.4), hip fracture (6.6%, RR = 1.3), myocardial infarction (3.5%, RR = 1.2), and ventricular arrhythmia (0.9%, RR = 1.1) [42]. It has, therefore, been concluded that it should be reserved for emergencies and delirium only [18].

SGAs have been found to increase mortality compared to placebo with a number needed to harm (NNH) of 73 [43]. There appears to be no difference in mortality between individually studied antipsychotics [25, 43], but the estimated mortality odds ratio was found to be the highest for olanzapine, followed by quetiapine, aripiprazole and risperidone [43]. Conversely, a case-control study by Maust et al. showed differences in NNH between risperidone (NNH = 27), olanzapine (NNH = 40), quetiapine (NNH = 50) as well as the FGA haloperidol (NNH = 26) [40].

3.2 Co-Prescribing of Other Medications and Antipsychotic-Related Mortality

A 2016 meta-analysis of all trials conducted with risperidone in people with dementia showed that co-prescribing of risperidone with anti-inflammatory medications increases risperidone versus placebo mortality risk [44]. Co-prescription of antipsychotics in patients taking antihypertensives, lipid-lowering drugs and antidiabetics including insulin may increase cardiovascular mortality, but is also associated with decreased risk of dying of cancer and infection [24]. Interactions between antipsychotics and other medications (such as antidepressants, opioids, benzodiazepines or cardiological medications) have also been shown to increase mortality among older adults with dementia [24, 45], and this risk increases with the number of interactions (one interaction: HR = 1.68; two or more interactions: HR = 1.96) [45]. The most common interactions are between antipsychotics (risperidone, tiapride and less commonly olanzapine) and cardiological medications (diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and less commonly calcium antagonists) resulting in decreased blood pressure and falls. Interactions with other psychotropic medications (benzodiazepines, opioids, antidepressants, carbamazepine) may lead to QT prolongation, sedation, cytochrome P450 inhibition and less commonly to anticholinergic effects, seizures and agranulocytosis [45]. Conditions pre-existing dementia, such as diabetes, heart disease and cerebrovascular disease, independently increase the mortality risk for patients taking antipsychotics in an additive manner [38].

It has been further demonstrated that patients with neuropsychiatric symptoms of dementia and co-morbid depression, have lower mortality when taking risperidone in monotherapy, compared to placebo[44]. Although this finding is not consistent—a Danish study by Nielsen et al. on a population of nearly 46,000 dementia patients found that those on various antipsychotics (most prescribed were risperidone, olanzapine, quetiapine, haloperidol, zuclopenthixol and chlorprothixene) with co-morbid psychiatric diagnoses, including depression, and/or somatic co-morbidities, have an increased risk of dying of infection, cardiovascular events and cancers, but not of intentional self-harm [24].

Although the exact mechanisms behind antipsychotic adverse effects are not known, there is evidence of risperidone interacting with immune and cardiac pathways, including selenium, on a cellular level [46, 47]. This highlights the importance of cardiovascular history screening and possible selenium deficiency screening.

3.3 Other Antipsychotic-Related Factors and Mortality

There is no consensus on how long the risk of adverse outcomes is increased for those patients, with data ranging from short- [36, 39, 42] to long-term [6, 15, 39]. Mortality may be the highest at the beginning of treatment. In line with previous research [40, 48], one retrospective cohort study demonstrated more than twofold increased mortality risk for antipsychotic initiators versus non-users in the first month of treatment, and significantly lower risks after 3 months (HR = 1.52) and 6 months (HR = 1.24) of follow-up [49]. The same study reported a higher mortality risk for robust versus frail (i.e., low Frailty Index scores) patients on antipsychotics at all three time points. This counterintuitive finding might potentially be related

to differences in baseline mortality risks of the evaluated cohorts. Other therapy-independent factors increasing the mortality risk are male sex, younger age at dementia diagnosis, as well as more severe dementia symptoms [24]. Factors increasing antipsychotic-related mortality are summarised in Table 1.

4 Other Antipsychotic-Related Adverse Events and Their Determinants

Unlike evidence for antipsychotic-related mortality, findings on other adverse outcomes are less consistent and detailed data on the relationship between individual medications, types of dementia and outcomes are often sparse (Table 2).

One consistent finding appears to be the association between the use of antipsychotics and CVEs, such as stroke and transient ischaemic attack [6, 7, 25, 28, 29, 50–53]. As a group, they have been found to increase the odds over twofold [50]. Particular agents implicated in an increased risk of CVE are risperidone and olanzapine, while quetiapine and aripiprazole carry risks similar to placebo [25, 28]. The relationship between antipsychotic use and CVE risk is complex and not yet fully understood. Koponen et al. found that the risk of stroke is increased within the first 60 days of use (HR = 2.61), but no significant increase was found after the follow-up period of 265 days [53]. One large naturalistic study on over 10,000 patients with dementia has shown different outcomes depending on whether the antipsychotic (FGA or SGA) was prescribed for psychosis and/or agitation, with an over twofold increased antipsychotic-related risk of CVEs for patients with dementia and psychosis but no agitation (HR = 2.16) [7]. The antipsychotic-related CVE risk was not increased in the patient group with agitation but no psychosis (HR = 1.10), or the group with agitation and psychosis (HR = 0.97). It has been hypothesised that

Table 1 Factors increasing antipsychotic-related mortality

Male sex [24]
Younger age at dementia diagnosis [24]
Severe dementia symptoms [24]
Robust build (low Frailty Index scores)[a] [49]
Number of co-morbid somatic conditions (cardiovascular, cancer, infection, diabetes, epilepsy, lower respiratory disease and others) [24, 38]
Co-morbid psychiatric conditions (psychosis, affective disorders, substance misuse, history of self-harm, and others)[24]
Depression co-morbid with agitation or psychosis was associated with lower mortality in risperidone monotherapy [44]
Polypharmacotherapy and drug interactions
– Anti-inflammatory medications, diuretics, ACE-inhibitors, beta-blockers, calcium-blockers, antidepressants, opioids, sedative agents, carbamazepine—all-cause/unspecified mortality [24, 44, 45]
– Antihypertensives, lipid-lowering drugs and antidiabetics including insulin—cardiovascular mortality (protective for death from cancer and infections) [24]

[a]Based on a retrospective cohort study with potential limitations [49]

ACE-inhibitor angiotensin-converting enzyme inhibitor, *FGA* first-generation antipsychotic, *SGA* second-generation antipsychotic

Table 2 Adverse outcomes of antipsychotics use in dementia patients

Consistent findings	Inconsistent findings
Cerebrovascular events [6, 7, 25, 28, 29, 50–53]	Cardiac events [51, 52]
Pneumonia [6, 54]	Fractures [29, 50, 51, 57]
Parkinsonian symptoms[a] [6, 25, 54]	Falls[d]
Gait disturbance [6]	
Sedation [6, 25, 54]	
Venous thromboembolisms [6, 51]	
Head injuries and traumatic brain injuries[b] [60]	
Increased mortality risk [20]	
Accelerated cognitive decline[c] [58]	

[a]With use of risperidone, but not olanzapine, aripiprazole and quetiapine

[b]Limited amount of evidence, this outcome is not included in meta-analyses

[c]Please note that presence of neuropsychiatric symptoms of dementia can also accelerate cognitive decline[6]

[d]Reports of increased risk [56], no association [28, 50] and reduced risk (for risperidone) [25]

tau protein may be linked to psychotic symptoms in AD as well as a toxic response to reduced brain perfusion, making patients suffering from antipsychotic-related sedation, dehydration or orthostatic hypotension more vulnerable to CVE. Psychosis in dementia is also linked to more advanced small vessel disease and cerebral amyloid angiopathy [7].

Other adverse outcomes associated with antipsychotic use in dementia include risk of extrapyramidal side effects including gait disturbance (with use of FGAs and risperidone, but less commonly olanzapine, aripiprazole, and quetiapine), sedation, venous thromboembolism, and pneumonia [6, 25, 51, 54]. Antipsychotics may be associated with pneumonia due to their effects on D_2, cholinergic and histamine receptors, leading to dysphagia (extrapyramidal side effect), sedation, involuntary buccolingual movements (a common symptom of tardive dyskinesia), and xerostomia; all of these factors, combined with changes in pulmonary secretion in older adults may increase the risk of pneumonia [54]. Movement side effects also play an important role in an increased risk of venous thromboembolism events that include deep vein thrombosis and pulmonary embolism—nigrostriatal D_2 receptor blockage causing muscle stiffness may lead to physical inactivity, akinesia [55] and prolonged time spent in bed. This, in addition to antipsychotic-related enhanced platelet aggregation and raised anticardiolipin antibodies, promotes blood clot formation [51]. Findings on increased risk of cardiac events, falls and fractures have been variable [25, 28, 29, 50–52, 56, 57]. In case of falls, evidence from four meta-analyses published between 2018 and 2020 vary significantly, with reports of increased risk of falls [56], no association with antipsychotics as a group [50] or individually for haloperidol, olanzapine, quetiapine and risperidone[28], to a reduced risk of falls with risperidone [25].

Dyer et al. found that being prescribed antipsychotics is linked to an accelerated cognitive decline among community-dwelling patients with mild to moderate AD (β coef: 3.89 after 18 months), with the risk even greater for APOE ε4 allele carriers (β coef: 4.96 after 18 months) [58]. Given that neuropsychiatric symptoms of dementia are also associated with more rapid cognitive decline [6] and are proportionate with the severity of AD [59], balancing the risk may complicate clinical decision making. Dyer et al. [58] highlighted, however, that in their study only half of the dementia participants were coded to have BPSD, and those with significant BPSD were excluded from the study.

One large cohort study looked at the association between antipsychotics and head injuries/ traumatic brain injuries [60]. The study reported an increased risk of head injuries among antipsychotic users compared to non-users, with the highest risk during the first 3 months of treatment. Quetiapine users had a higher rate of head injuries than risperidone users, which was attributed to quetiapine being more sedative and having a higher risk of orthostatic hypotension leading to falls.

Little is known about adverse outcomes risk in various types of dementia; however, there is evidence that patients with dementia with Lewy bodies (DLB) or frontotemporal degeneration (FTD) are at even higher risk of antipsychotic side effects. Due to neuroleptic hypersensitivity, DLB patients are more susceptible to extrapyramidal side effects, and in some cases have been associated with irreversible cognitive decline and death. In these patients FGAs are contraindicated, and SGAs such as olanzapine, risperidone and aripiprazole should be avoided due to their potential to worsen motor symptoms. With caution, quetiapine and clozapine can be used [18]. Reviews of literature focused on the management of psychosis in DLB and Parkinson's disease dementia [61, 62] report positive treatment results using acetylcholinesterase inhibitors and pimavanserin. A 2014 randomised controlled trial on pimavanserin in Parkinson's disease patients with psychotic symptoms showed favourable clinical outcomes (37% improvement of symptoms in the pimavanserin arm vs. 14% in the placebo arm) without exacerbation of motor symptoms or sedation [63].

The evidence is also scarce for antipsychotic use in patients with FTD other than increased sensitivity to antipsychotics side effects [18], therefore a reasonable solution may be to follow a similar treatment pathway to that for DLB. Although no specific titration or monitoring recommendations for DLB and FTD patients have been published, in these patient groups it is especially important to observe the "start low, go slow" rule.

There has also been limited information on the efficacy and safety of antipsychotics in dementia patients with functional impairment and BPSD. A 2022 systematic review looking into this specific group of patients concluded that due to lack of evidence, no specific treatment recommendations can be made [19].

Finally, the older population remains at a higher risk of the general side effects of antipsychotics due to pharmacokinetic and pharmacodynamic age-related changes such as reduced renal and hepatic clearance and first-pass metabolism, a smaller volume of distribution for hydrophilic medication, and increased risk for lipophilic drugs causing prolonged elimination of some medications. Receptors' sensitivity to medication can also be altered with progressing age. All of these natural ageing processes make dementia patients more susceptible to side effects such as QT prolongation, weight gain and metabolic syndrome, anticholinergic effects, seizures or orthostatic hypotension [55, 64].

5 Associations of Adverse Effects of Antipsychotic Medications with Health Service Outcomes

5.1 Hospital Treatment

Medications' adverse outcomes are associated with emergency department presentations, with older adults being three times more likely than younger patients to visit the emergency department due to adverse drug events [65]. Among older adults, those with AD have a higher proportion of visits associated with psychotropic-related adverse drug events compared to non-AD patients (1.04% and 0.43%, respectively). These are mostly associated with antipsychotics and benzodiazepines. Patients with AD seen in the emergency department with psychotropic medication-related adverse events are more likely to be subsequently admitted to hospital compared to non-AD patients. Once admitted, AD patients have on average longer hospitalisations and higher in-hospital mortality [65]. Zakarias et al. have also reported a 55% increase in hospitalisations for patients co-prescribed antipsychotics and benzodiazepines in comparison to antipsychotic monotherapy, but no increase was found for co-prescription of antipsychotics with antidepressants [57]. This study did not, however, investigate the hospitalisation rates of patients not being prescribed antipsychotics.

A Finnish study on AD patients with a 2-year follow-up found that the antipsychotic group (mean age 81.5 years) had spent more days in the hospital compared to the non-antipsychotic group (15 vs. 7 days, respectively) [66]. In this study population, significantly more of the non-antipsychotic group had no hospitalisations at all compared to those on antipsychotics. The antipsychotic group had higher rates of admissions with diagnostic codes for dementia, mental and behavioural disorders, diseases of respiratory, genitourinary and cardiovascular systems, and certain infections. In the as-treated analysis, patients on antipsychotics had more inpatient days due to injuries and poisonings. Seventy percent of the antipsychotic group had caregivers' care breaks recorded as an additional reason for admission.

5.2 Long-Term Care and Institutionalisation

Another concern for patients with dementia is their dependence on long-term care, including admission to a nursing home. There is evidence that treatment with antipsychotic medications significantly increases the risk of reliance on long-term care and institutionalisation. A twofold risk of long-term care dependency has been reported for patients receiving risperidone, melperone, haloperidol or other FGAs in 18-month follow-up; the risk for quetiapine was slightly lower. The rate of nursing home admissions was increased for those taking quetiapine, risperidone, melperone, haloperidol and other FGAs. Other studied SGAs (amisulpride, zotepine, ziprasidone, aripiprazole, sertindole, olanzapine and clozapine) have not been shown to increase the risk of long-term care dependency or nursing home admission [67].

5.3 Cost-Effectiveness of Treatment

Huo et al. conducted a systematic review of the cost-effectiveness of pharmacotherapy in persons with dementia [68]. They concluded that neither antipsychotics nor antidepressants, which are commonly used to treat neuropsychiatric symptoms of dementia, were associated with lower healthcare cost. This raises further questions about the rationale for antipsychotic use in older adults with dementia. It is important to note that these findings are based on just two studies that investigated the cost-effectiveness of antipsychotics and antidepressants, published in 2007 and 2013. Given the worldwide economic and healthcare changes since that time, new studies on cost-effectiveness are needed. The health service outcomes are summarised in Table 3.

6 Implications of Antipsychotic Prescribing Practices in People with Dementia

Management of neuropsychiatric symptoms remains one of the main challenges in the treatment of older adults with dementia. Symptoms such as agitation, aggression, impulsivity and irritability are commonly managed with antipsychotics, although it is recommended to explore non-pharmacological interventions and pain management [69] first. Non-pharmacological treatment for BPSD is often referred to as the "eco-bio-psycho-social" approach [4]. Important aspects of this approach are to reduce under- or overstimulation in a person's environment, re-orientate them to the time, place and circumstances, and build meaningful relationships. Use of reminiscence therapy (bringing back positive memories from the past), validation therapy, aromatherapy, Snoezelen (soothing and stimulating surroundings), and acupuncture are other suggested techniques [4, 70, 71]. Similar to studies on medications, research on the non-pharmacological treatment of BPSD does not provide a clear answer on the single best approach, its choice or implementation. It is often left to individual considerations and preferences of caregivers [4, 71, 72]. Various psychotropic medications have been studied to address the neuropsychiatric symptoms of dementia, including antipsychotics, antidepressants, anticonvulsants (often used as mood stabilizers in psychiatry), benzodiazepines, acetylcholinesterase inhibitors, memantine, dextromethorphan with quinidine, prazosin, cannabinoids and buspirone; however, none of these are considered both safe and effective in addressing agitation and psychotic

Table 3 Antipsychotic-related health service outcomes

AD patients have more emergency department visits due to medication adverse events than non-AD patients and are more likely to be admitted to the hospital [65]
AD patients with adverse drug events have longer hospitalisations and higher in-hospital mortality compared to non-AD patients [65] and patients who do not take antipsychotics [66]
Co-prescribing benzodiazepines and antipsychotics significantly increases hospitalisation rates compared to antipsychotic monotherapy [57]
Dementia patients taking antipsychotics have higher rates of hospital admissions with infections, diseases of respiratory, genitourinary and cardiovascular systems, as well as mental and behavioural disorders [66]
Treatment with antipsychotics may increase the risk of reliance on long-term care and institutionalisation for patients with dementia [67]
Treatment with antipsychotics does not reduce healthcare costs [68]

AD Alzheimer's disease

symptoms in dementia. Although evidence for therapeutic benefits exists for selective serotonin-reuptake inhibitors (SSRIs) and antipsychotics, they address different neuropsychiatric symptoms, and evidence for SSRIs has been inconsistent. A 2011 Cochrane Systematic Review by Seitz et al. on the use of antidepressants for agitation in dementia reported that of five studies comparing SSRIs to placebo, only two showed a reduction of symptoms with use of sertraline and citalopram [73]. Notably, one study included in that review compared the use of citalopram and risperidone and found no difference between these agents in Neurobehavioural Rating Scale scores. A 2018 meta-analysis [74] found that the effectiveness of risperidone and SSRIs versus placebo are comparable (OR 1.96 and 1.61, respectively).

Based on our literature review, there seems to be no single antipsychotic that is considered both safe and effective for the management of agitation and psychosis in dementia (Table 4, "take home messages"). Data on the risk of those serious consequences of treatment are often contradictory [10, 25, 28]. Due to the side effect profiles and mortality risk, many authors recommend using SGAs over FGAs [6, 18, 39, 41, 42, 51, 54]; however, the growing evidence suggests that the difference between these groups may be less significant than previously believed [20]. Clinicians must take an individual approach to prescribing, weighing up potential benefits and risks of individual medications in the context of the patient's symptoms, circumstances, prescribed medications and co-morbidities. Such a nuanced approach might reduce the risk; however, formal evidence to support decision-making is scarce [18, 25, 28, 50–52]. Antipsychotic use in older adults with dementia is associated with an increased risk of significant adverse events such as stroke or transient ischaemic attacks, venous thromboembolism, pneumonia, head and brain injuries, as well as death. SGAs are also closely related to the risk of metabolic syndrome and cardiovascular risk. Their use, alongside the presence of a severe mental illness, has been included in the QRISK®3 algorithm used in the UK to estimate the 10-year risk of heart attack or stroke. It has been shown that the use of SGAs is associated with a 29% increased cardiovascular risk in women and 15% in men compared to the general population [75]. Although these numbers do

Table 4 Take-home messages on the implications of adverse outcomes associated with antipsychotics in older patients with dementia

The use of antipsychotics in older adults with dementia can reduce agitation, psychosis, and associated distress; however, no medication is considered safe in this population
Antipsychotics are generally associated with an increased risk of mortality and cerebrovascular events
Due to slightly higher risk of mortality and cardiovascular and extrapyramidal side effects compared to second-generation antipsychotics, first-generation antipsychotics should be reserved for emergencies
Antipsychotic-related mortality may be higher at the beginning of treatment, hence a thorough risk-benefit assessment including cardiovascular risk should be conducted before commencing these medications
The risk does, however, remain increased throughout the treatment (evidence for up to 6 years [39]); the need for continuation of antipsychotics should be regularly reviewed and medication ceased as soon as possible. Withdrawing antipsychotic therapy may improve long-term survival and is not associated with relapse of agitation and psychosis
Antipsychotic treatment is associated with higher rates of hospitalisations and dependency on long-term care, including care home admissions
Use of antipsychotics may not be cost-efficient for healthcare systems
Treatment with antipsychotics requires physical health monitoring. In the absence of dementia-specific monitoring requirements, older adults with dementia should follow the same recommendations as the general patient population
Despite the clear risks of using antipsychotics in dementia patients, their risk-benefit balance makes them preferable to other psychotropic medications

not directly refer to the dementia population, they highlight the additional risk for the vulnerable old age group. On the other hand, the neuropsychiatric symptoms of dementia—agitation, depression and psychosis in particular—are associated with rapid dementia progression, institutionalisation and increased mortality [76, 77], therefore, they need to be effectively managed to improve outcomes for the patients.

Importantly, there is no safe time frame for use of antipsychotics in older adults with dementia—both short-term and long-term prescriptions are potentially harmful [6, 15, 24, 36, 37, 39, 42]. A 2018 systematic review concluded that antipsychotic treatment may be successfully discontinued with little to no difference to overall neuropsychiatric symptoms, adverse events, quality of life and cognitive function. Due to limited data, the effect of discontinuation on mortality could not be established [78].

Regular physical health monitoring may be one of the ways to reduce the risk of adverse events and mortality. The UK's NICE recommends regular checks of body weight, pulse, blood pressure, ECG (with QTc assessment), screening for the presence of movement disorders, as well as blood tests including full blood count, electrolytes and kidney function tests, liver function tests, lipid profile, HbA1c/blood glucose, and prolactin. Notably, monitoring is more frequent at the beginning of treatment with weekly weight checks over the first 6 weeks, blood test panels, weight check and lifestyle review after the initial 3 months of treatment, and then annually [79]. This guidance has, however, been created for adult patients; older adults may require closer monitoring, depending on individual needs and at the clinician's discretion. Although there have been multiple studies into the benefits and risks of the use of antipsychotics in dementia patients, there are no validated tools supporting individual decision making, which is an important research area to be explored.

Declarations

Conflict of interest RS has received research support from Janssen, GSK and Takeda. DA has received research support and/or honoraria from Astra-Zeneca, H. Lundbeck, Novartis Pharmaceuticals and GE Health, and serves as a paid consultant for H. Lundbeck and Axovant. CB has received honoraria and grant funding from Acadia Pharmaceuticals, Lundbeck, Takeda and Axovant pharmaceutical companies. CB leads the Alzheimer's disease psychosis (ADP) investigators group and has received honoraria from Lundbeck, Lilly, Otusaka and Orion pharmaceutical companies. MR, MT, BC, LV, KT and CM declare no conflicts of interest.

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Author contributions MR: Review of literature, interpretation of data, preparation of the manuscript, and critical revision for intellectual content. CM: Article concept and design, interpretation of data, and critical revision of the manuscript for intellectual content. BC, LV, DA, CB, KT, RS: Interpretation of data and critical revision of the manuscript for intellectual content. MT: Critical revision for intellectual content, preparation of the manuscript. All authors approved the manuscript to be published and agree to be accountable for all aspects of the work.

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